Electrophilic Substitution in Indoles. Part VIII.[1] The Mechanism of Electrophilic Substitution in 6-Methoxyindoles †

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Deuterium and tritium labelling experiments show that the boron trifluoride-catalysed cyclisation of 4-(6-methoxyindol-3-yl)butanol to 7-methoxytetrahydrocarbazole occurs by two simultaneous pathways. The major route involves initial cyclisation at the 3-position to give an intermediate spirocyclic indolenine salt which then rearranges to the tetrahydrocarbazole: the minor pathway involves direct attack at the 2-position. A similar duality of mechanism occurs in the solvolysis of the corresponding methoxyindolylbutyl tosylate.

ELECTROPHILIC substitution in indoles normally occurs at the 3-position,[2] and this has been demonstrated to hold even in cases in which the 3-position is already substituted by an alkyl group.[3] Thus, by tritium labelling, we have shown [3] that in the boron trifluoride-catalysed cyclisation of the indolylbutanol (1a) to the tetrahydrocarbazole (3a) the indolenine-3-spirocyclopentane (2a) is an intermediate. Whilst this mechanism may be a general one for simple indoles, there is evidence[4] to suggest that a methoxy-group in the 6-position of the indole nucleus can activate the 2-position (in preference to the 3-position) towards electrophilic attack as shown in (4). For example, on allowing 6-methoxytryptamine and acetone to stand in acetate buffer (pH 4·7) for seven days at room temperature, the tetrahydro-β-carboline (5) was obtained by Hester [4a] in 93% yield; when the reaction was repeated with tryptamine itself or 5-methoxytryptamine no tetrahydrocarboline at all was formed.[4a] The electronic effects of the 6-methoxy-group are also probably responsible for the ready epimerisation of reserpine which occurs at C-3 under acidic conditions in which protonation at the 2-position has been implicated; [4b] [3-^{2}H]reserpine (6a) undergoes epimerisation in boiling glacial acetic acid at C-3 without loss of label whereas the demethoxy-analogue, [3-^{2}H]deserpine (6b) undergoes both epimerisation and loss of label.

In the light of these results we decided to investigate the effect of a 6-methoxy-group on the electrophilic substitution of indole by examining the boron trifluoride-

† Preliminary report, R. Iyer, A. H. Jackson, P. V. R. Shannon, and B. Naidoo, *Chem. Comm.*, 1972, 461.

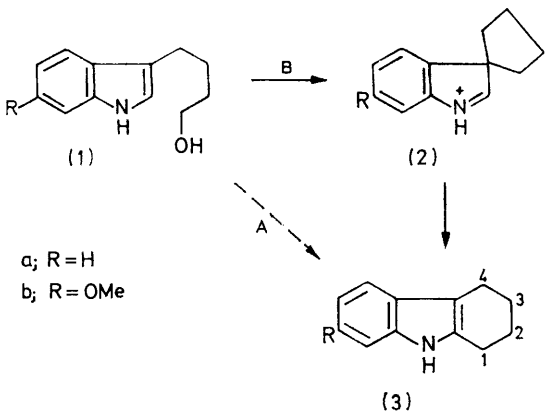
[1] Part VII, A. H. Jackson and B. Naidoo, *J.C.S. Perkin II*, 1973, 548.

[2] (*a*) R. J. Sundberg, 'The Chemistry of Indoles,' Academic Press, New York, 1970, ch. 1; (*b*) R. M. Acheson, 'Introduction to the Chemistry of Heterocyclic Compounds,' Interscience, New York, 1967, p. 131.

[3] A. H. Jackson, B. Naidoo, and P. Smith, *Tetrahedron*, 1968, **24**, 6119.

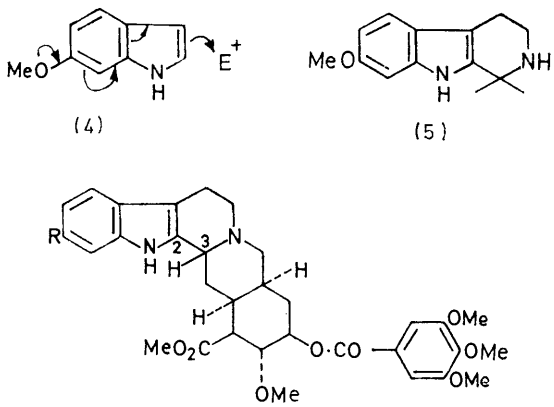
[4] (*a*) J. B. Hester, *J. Org. Chem.*, 1964, **29**, 2864; (*b*) A. J. Gaskell and J. A. Joule, *Tetrahedron*, 1967, **23**, 4053.

catalysed cyclisation of 4-(6-methoxyindol-3-yl)butanol (1b), to the corresponding tetrahydrocarbazole (3b).



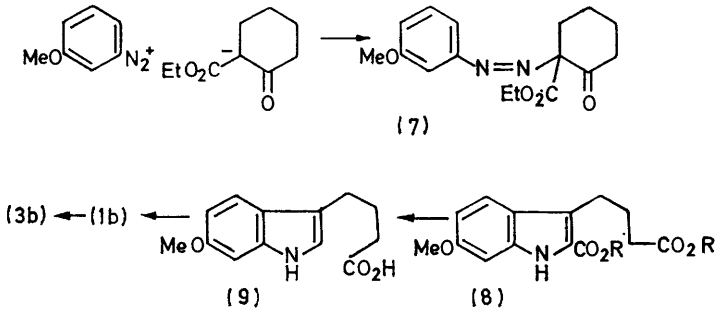
SCHEME 1

A number of methods for synthesising indole derivatives related to (1b) were investigated but most of them



were unsuccessful, *e.g.* cyclisation of the *m*-methoxyphenylhydrazone of δ-formylvalerate only gave traces of indole.[5] However, Japp–Klingemann condensation of *m*-methoxybenzenediazonium fluoroborate and the sodium salt of ethyl 2-oxocyclohexanecarboxylate in ethanol (see Scheme 2) gave the azo-intermediate (7) which was cyclised with ethanolic hydrogen chloride to the diester (8; R = Et); initial attempts to cyclise the intermediate (7) under aqueous conditions afforded little or no indole. Hydrolysis of the diester (8; R = Et) afforded the corresponding diacid (8; R = H) which was carefully thermally decarboxylated to the monoacid (9). Reduction of the latter with diborane or lithium aluminium hydride afforded the required methoxyindolylbutanol (1b) which was cyclised to the known [6] 7-methoxytetrahydrocarbazole (3b) by refluxing boron trifluoride–ether. Slight differences between various n.m.r. spectra ($CDCl_3$) of the tetrahydrocarbazole (3b) were observed, and it was shown that these differences could be explained by the presence of traces of acid in the solvent (see Experimental section for details). However, a very similar effect was also observed with tetrahydrocarbazole itself (3a), and both effects were in keeping with at least partial protonation at the 3-position of the indole nucleus to generate the ions (10a) or (10b).

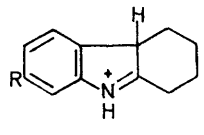
To prepare a suitably labelled substrate (1b) for the cyclisation experiments, the methoxyindolylbutyric acid (9) was reduced with tritiated diborane, generated from tritiated sodium borohydride and iodine, and the resulting alcohol was purified by chromatography before dilution with pure inactive material. The tritiated alcohol was readily cyclised in refluxing boron trifluoride–ether and the resulting mixture of tritiated 7-methoxytetrahydrocarbazoles was isolated by chromatography, and crystallised to constant activity. To compare the relative activities at the 1- and 4-positions in the tetrahydrocarbazoles, the periodic acid oxidation (*cf.* ref. 7) to the 1-oxo-derivative (11a) was studied. However, two products were obtained, the 1-oxo-6-iodo-derivative (11b) (9%) and the iodo-oxo-amide (12b) (40%). This contrasts markedly with the periodic acid oxidation of tetrahydrocarbazole (3a) itself which affords a 62% yield of the 1-oxo-derivative;[3,7] the related oxo-amide is only obtained with sodium metaperiodate oxidation.[7] However, these results must be attributed to the increased activation of the 2,3-double bond in the indole nucleus caused by the methoxy-group; the insertion of



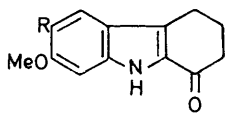
SCHEME 2

[5] E. Baer, *J. Amer. Chem. Soc.*, 1942, **64**, 1417.
[6] J. R. Chalmers, H. T. Openshaw, and G. F. Smith, *J. Chem. Soc.*, 1957, 1115.
[7] L. J. Dolby and D. L. Booth, *J. Amer. Chem. Soc.*, 1966, **88**, 1049.

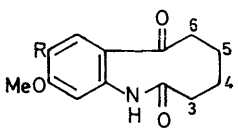
iodine (formed in the reaction) in the benzene ring is also facilitated by the methoxy-group. The relative molar activity of the iodo-oxo derivative (11b) after crystallisation to constant activity was 48% of that of the parent tetrahydrocarbazole (3b). This preliminary result indicated the possibility that two reaction pathways occurred



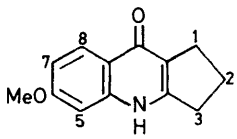
(10) a; R = H
b; R = OMe



(11) a; R = H
b; R = I



(12) a; R = H
b; R = I



(13)

during the cyclisation reaction (1b) ⟶ (3b), 4·5% by direct substitution at the 2-position (path A in the Scheme 1) and 95·5% by the indirect route involving initial substitution at the 3-position (path B).

Three further experiments on the cyclisation were carried out and the results are summarised in the Table, together with a further result arising from an early attempt to prepare the tosylate of the alcohol (1b) for studies of its solvolysis. We had hoped to prepare this tosylate in the same manner as its demethoxy analogue (*i.e.* by treatment of the alcohol with toluene-*p*-sulphonyl chloride in dry pyridine at −40°) but in the event the only product isolated was the 7-methoxytetrahydrocarbazole (3b). The tosylate was presumably formed as an intermediate in this reaction but then cyclised immediately, or during the work-up, owing to the additional activation of the indole nucleus afforded by the methoxy-group, as compared with the unsubstituted analogue.

Relative molar activities of methoxytetrahydrocarbazole (3b) and its 1-oxo-derivative (11b) derived from various cyclisations of [1-^{3}H]-4-(6-methoxyindol-3-yl)butan-1-ol (1b)

Expt.	Cyclisation reagent	Temp. (°C)	Time (min)	Relative molar activity (11b)/(3b)	Direct substitution (path A, Scheme 1) (%)
1	BF_3–Et_2O	126	45	0·477	4·5
2	BF_3–Et_2O	126	30	0·385	22·0
3	BF_3–Et_2O	100	45	0·430	14·0
4	TsCl–pyridine	20 †	†	0·365	27·0

† Cyclisation presumably occurred *via* the tosylate (see text and Experimental section).

It will be seen from the Table that the lower the temperature, and the shorter the time of reaction (in the case of the boron trifluoride-catalysed cyclisations of the alcohol) then the greater the apparent percentage of direct 2-substitution. The only explanation for this phenomenon was that the methoxytetrahydrocarbazole (3b) once formed, undergoes acid-catalysed equilibration with the spirocyclic indolenine (2b), whereas our earlier work[3] had clearly ruled out such a process in the demethoxy-series. This interpretation was confirmed by subsequent work (see following paper) in which we found that the extent of equilibration was negligible below 100°. However, at this stage in our investigations we turned to the use of deuterium rather than tritium labelling owing to the difficulties in obtaining good yields of the 1-oxo-compound (11b). We found that the 7-methoxytetrahydrocarbazole (3b) was readily cleaved by sodium metaperiodate to the oxo-amide (12a) in good yield and furthermore that the resonances of the methylene protons neighbouring the two carbonyl groups were quite separate in the n.m.r. spectrum. (In the parent tetrahydrocarbazole the 1- and 4-methylene proton resonances are superimposed on one another).

The methoxyindolylbutanol (1b), labelled with deuterium in the methylene group next to the hydroxy-function, was prepared by lithium aluminium deuteride reduction of the corresponding carboxylic acid (9), and cyclised with boron trifluoride-ether at 80° (*i.e.* well below the temperature at which equilibration of the methoxytetrahydrocarbazole occurs). After their isolation by chromatography, oxidation of the deuteriotetrahydrocarbazoles with sodium metaperiodate then gave the deuteriated amides (12a) and the percentage of deuterium in each of the two appropriate methylene groups was estimated from their resonances in the n.m.r. spectrum (in trifluoroacetic acid). The specific assignments were initially made tentatively on the basis of comparisons with the positions of the methyl signals in the spectra of acetanilide and acetophenone (τ 7·57 and 7·36 respectively in trifluoroacetic acid). These were later confirmed by experiments with 7-methoxytetrahydrocarbazole specifically deuteriated at the 1-position (see following paper). The oxo-amide (12a) on heating underwent a ready cyclisation to the quinolone (13) in which only the two hydrogen atoms at C-6 in (12a) were eliminated, as observed previously in the demethoxy-series and in analogous compounds under basic conditions.[8] We also observed that the same reaction slowly occurred in the trifluoroacetic acid solution used for the n.m.r. measurements of (12a), but took about one month at 20° to go to completion. For this reason n.m.r. studies of the oxo-amide (12a) were always carried out immediately after preparing the solution. N.m.r. shift reagents were ineffective with tetrahydrocarbazole.

The results of the n.m.r. studies on the oxo-amide (12a) derived from the 1,1-dideuteriated alcohol (1b) (see Experimental section) showed that the initial

[8] (*a*) B. Witkop and S. Goodwin, *J. Amer. Chem. Soc.*, 1953, **75**, 3371; (*b*) B. Witkop, J. B. Patrick, and M. Rosenblum, *ibid.*, 1951, **73**, 2641.

cyclisation reaction involved 27% direct attack at the 2-position and 73% indirect attack at the 3-position. These figures are in good agreement with those derived from the experiments involving the cyclisation of the tosylate of the tritiated alcohol (1b); the latter cyclisation must have occurred at room temperature, or below, and hence no equilibration with the spirocyclic indolenine could have occurred.

Our results thus clearly confirm the suggestion that a 6-methoxy-group can sufficiently activate the 2-position of the indole nucleus so that it becomes a significantly competitive site of attack to the normal 3-position in electrophilic substitution reactions. Analogous activation of the 2-position is known in electrophilic substitution of 6-alkoxybenzothiophens.[9]

The extent to which this effect, and the equilibration of the tetrahydrocarbazole with the spirocyclic indolenine salt is influenced by the presence of a second methoxy-group in the indole 4-position is currently under investigation. The results in the monomethoxy-series are however of general interest not only in connection with the basic chemistry of the indole nucleus, but also in relation to attempts to synthesise indole alkaloids and their analogues, especially those bearing a methoxy-group at the 6-position.[10,11]

EXPERIMENTAL

Mass spectra were obtained on a Varian CH5-D instrument at 70 eV. N.m.r. spectra were measured at 100 MHz on a Perkin-Elmer R14 spectrometer in $CDCl_3$ unless stated otherwise; u.v. spectra were determined in spectroscopic ethanol on a Unicam SP 800 spectrophotometer and i.r. spectra were measured on a Unicam SP 200G grating i.r. spectrophotometer. Light petroleum refers to that of boiling range 40—60°. Activities were measured by scintillation counting with a Packard 'Tri-Carb' liquid scintillation spectrometer. Solute samples were dissolved in a solution of 2,5-diphenyloxazole (5 g), 1,4-bis-2-(4-methyl-5-phenyloxazolyl)benzene (0·3 g), and AnalaR toluene (1 l). The efficiency was estimated by the addition of a known quantity of an internal standard of [1,2-$^3H_2$]-n-hexadecane of specific activity 2·47 μCi g^{-1}. T.l.c. and p.l.c. was carried out with plates made up from Kieselgel HF 254 (Merck). For quantitative n.m.r. measurements on deuteriated compounds, the proton resonance signal areas were expanded and measured by tracing and weighing. A minimum of five traces was used and the experimental error was approximately ±1·5%.

m-*Methoxybenzenediazonium Fluoroborate*.—*m*-Anisidine (8·2 g; b.p. 80—82° at 0·5 mmHg; freshly distilled) was stirred at 0—5° in hydrochloric acid (48 ml) and water (48 ml). A white precipitate separated. Sodium nitrite (4·8 g) in water (20 ml) was added dropwise with stirring the temperature being maintained at 0—5°. To the resulting clear red solution was added sodium fluoroborate (7·2 g) in water (16 ml) and a yellow solid immediately separated from the solution. The mixture was kept at 20° for 10 min and the solid was filtered and washed with water (3 × 30 ml), methanol (2 × 30 ml), and ether (4 × 30 ml) before drying (0·5 mmHg and 1 h) to give the fluoroborate salt as a buff coloured solid (10·3 g, 72%).

Ethyl 4-(2-*Ethoxycarbonyl*-6-*methoxyindol*-3-*yl*)*butyrate* (8; R = Et).—To a suspension of sodium hydride (0·5 g; 1 g of 50% dispersion in oil) in dry tetrahydrofuran (THF) (25 ml) under nitrogen was added slowly a solution of ethyl 2-oxocyclohexanecarboxylate (3·11 g)[12] in dry THF (30 ml) A clear yellow solution of the anion resulted. The mixture was refluxed for 30 min and after cooling to −5° the above dry diazonium fluoroborate salt (4·0 g) was added in portions with stirring. The solution turned red and a yellow deposit of sodium fluoroborate appeared. The mixture was then stirred for 1 h at 20°, poured into water (200 ml), and extracted with ether (3 × 100 ml). The combined extracts were washed with water (100 ml) and dried ($MgSO_4$). Removal of solvent under reduced pressure at 25° afforded ethyl 1-(3-methoxyphenylazo)-2-oxocyclohexanecarboxylate (7) as a red oil (6·5 g), τ 8·75 (3H, *t*, *J* 7 Hz, CH_2CH_3), 8·2 (4H, m, $CO{\cdot}CH_2{,}CH_2CH_2$), 7·4 (2H, m, $CO{\cdot}CH_2{\cdot}CH_2$), 6·22 (3H, s, OMe), 5·76 (2H, q, *J* 7 Hz, OCH_2CH_3), 2·93 (1H, m, ArH), and 2·66 (3H, m, ArH), $\lambda_{max.}$ 235 (ε 10,940), 280 (8390), and 330 nm (3160). The crude product was used immediately for the next stage. A solution in ethanol (80 ml) was saturated with HCl gas and the solution was refluxed for 15 min before keeping overnight at 20°. The mixture was then diluted with water (200 ml) and extracted with chloroform (2 × 100 ml). The extract was washed with water (100 ml), dried ($MgSO_4$), and removal of solvent under reduced pressure gave the crude diester as a yellow syrup. Crystallisation from petroleum ether (b.p. 60—80°) gave the *diester* (8; R = Et) (5·2 g), m.p. 77—78°, τ 8·76 (3H, t, *J* 7 Hz, CH_2CH_3), 8·57 (3H, t, *J* 7 Hz, $IndCO_2CH_2CH_3$), 7·97 (2H, m, $CH_2CH_2CH_2$), 7·63 (2H, t, *J* 7 Hz, CH_2CO_2Et), 6·84 (2H, t, *J* 7 Hz, $IndCH_2$), 6·13 (3H, s, OMe), 5·86 (2H, q, *J* 7 Hz, CH_2CH_3), 5·57 (2H, q, *J* 7 Hz, $IndCO_2CH_2$), 3·18 (1H, s, Ind-7-H), 3·13 (1H, dd, *J* 10, 2 Hz, Ind-5-H), 2·39 (1H, d, *J* 10 Hz, Ind-4-H), and 1·23br (1H, s, NH), $\lambda_{max.}$ 225 (ε 20,890), 250 (13,180), 260sh (10,000), and 317 (19,950) nm, *m/e* (%) 333 (M^+ 100) 288 (30), 260 (33), 245 (33), 232 (73), 214 (23), 200 (17), 199 (20), 186 (80), 158 (33), 144 (10), 143 (10), 128 (12), 115 (15), and 89 (10) (Found: C, 65·0; H, 7·2; N, 4·3. $C_{18}H_{23}NO_5$ requires C, 64·8; H, 6·9; N, 4·2%).

(2-*Carboxy*-6-*methoxyindol*-3-*yl*)*butyric Acid* (8; R = H). —The above diester (10 g) in ethanol (225 ml) containing sodium hydroxide (5 g) was heated under reflux for 30 min. The sodium salt of the diacid separated out from the mixture. The mixture was then poured into water (100 ml) and ethanol removed under reduced pressure. Sulphur dioxide was passed through the residual aqueous solution when the diacid precipitated as a cream solid. Crystallisation from methanol gave the *diacid* (8; R = H) (7 g, 80%) as off-white crystals, m.p. 223—224° (decomp.), τ ($CDCl_3$–[$^2H_6$]DMSO) 8·0 (2H, m, $CH_2CH_2CO_2H$), 7·7 (2H, t, *J* 8 Hz, CH_2CO_2H), 6·86 (2H, t, *J* 8 Hz, $CH_2CH_2CH_2CO_2H$), 6·2 (3H, s, OMe), 3·32 (1H, dd, *J* 9, 1 Hz, Ind-5-H), 3·19 (1H, d, *J* 1 Hz, Ind-7-H), 2·66br (2H, s, 2 × CO_2H) 2·51 (1H, d, *J* 9 Hz, Ind-4-H), and 0·2br (1H, s, NH), $\lambda_{max.}$ 225 (ε 19,050), 250 (12,880), 258sh (10,230), 310 (17,780), and 320sh (17,780) nm, $\nu_{max.}$ (CCl_4) 3333 (NH), 2630br (OH), 1724, and 1667 (C=O) cm^{-1}, *m/e* (%) 277 (M^+, 100), 233 (13), 232 (15), 204 (60), 199 (13), 186 (79), 160 (22), 158 (25),

[9] E. Campaigne and W. E. Kreighbaum, *J. Org. Chem.*, 1961, **26**, 363.
[10] A. H. Jackson and A. E. Smith, *Tetrahedron*, 1968, **24**, 403.
[11] *Cf.* G. Buchi, K. E. Matsumoto, and H. Nishimura, *J. Amer. Chem. Soc.*, 1971, **93**, 3299.
[12] *Org. Synth.*, 1943, **2**, 531.

112 (13), 99 (37), and 81 (25) (Found: C, 60·8; H, 5·4; N, 5·0. $C_{14}H_{15}NO_5$ requires C, 60·6; H, 5·4; N, 5·0%).

4-(6-*Methoxyindol*-3-*yl*)*butyric Acid* (9).—The above diacid (7 g) was divided into portions (1 g) which were each cautiously heated in a conical flask until effervescence ceased. The combined residues were crystallised twice from benzene to give the required *acid* (9) as pale yellow crystals (4·5 g, 75%), m.p. 136—138°, τ ($CDCl_3$–[$^2H_6$]DMSO) 8·0 (2H, quintet, *J* 7 Hz, $IndCH_2CH_2$), 7·65 (2H, t, *J* 7 Hz, CH_2CO_2H), 7·25 (2H, t, *J* 7 Hz, Ind-CH_2), 6·22 (3H, s, OMe), 3·33 (1H, dd, *J* 9, 2 Hz, Ind-5-H), 3·21br (2H, s, Ind-2-H and -7-H), 2·63 (1H, d, *J* 9 Hz, Ind-4-H), 1·21br (1H, s, CO_2H), and 1·1br (1H, s, NH), $\lambda_{max.}$ 229 (ε 20,420), 272 (5495), and 290 (5248) nm, *m/e* (%) 233 (M^+, 36), 215 (14), 173 (10), 172 (9), 160 (100), 145 (20), 130 (12), 117 (20), 97 (10), and 83 (10) (Found: C, 67·0; H, 6·7; N, 6·0. $C_{13}H_{15}NO_3$ requires C, 66·9; H, 6·5; N, 6·0%).

4-(6-*Methoxyindol*-3-*yl*)*butan*-1-*ol* (1b).—(a) *From lithium aluminium hydride reduction.* Lithium aluminium hydride (100 mg) was suspended in dry THF (10 ml) and a solution of the above monoacid (0·3 g) in dry THF (10 ml) was added dropwise. After the addition the mixture was heated under reflux for 15 min and then cooled to 20° before the complex was decomposed with saturated Rochelle salt solution. The mixture was poured into water (50 ml) and extracted with ether (3 × 50 ml). The extract was washed with water (50 ml), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The solid residue was crystallised from benzene to give the *alcohol* (1b) as off-white plates (0·2 g, 66%) m.p. 86—87°, τ 8·5br (1H, s, OH), 8·34 (4H, m, $IndCH_2CH_2CH_2$), 7·3 (2H, t, *J* 8 Hz, $IndCH_2$), 6·39 (2H, t, *J* 7 Hz, CH_2OH), 6·2 (3H, s, OMe), 3·26 (1H, partially obscured dd, ^4J 2 Hz, Ind-5-H), 3·24br (2H, s, Ind-2-H and -7-H), 2·59 (1H, d, *J* 9 Hz, Ind-4-H), and 2·2br (1H, s, NH), $\lambda_{max.}$ 227 (ε 26,300), 270 (6760), and 290 (6170) nm, $\nu_{max.}$ (Nujol) 3333 (NH) and 3175 (OH) cm^{-1}, *m/e* (%) 219 (M^+, 51), 200 (3), 174 (8), 161 (22), 160 (100), 148 (7), 145 (16), 130 (4), 117 (14), 90 (5), and 89 (5) (Found: C, 71·4; H, 8·0; N, 6·5. $C_{13}H_{17}NO_2$ requires C, 71·2; H, 7·8; N, 6·4%).

(b) *By diborane reduction.* Diborane, generated from sodium borohydride (1·0 g) in dry diglyme (50 ml) and iodine (3·1 g) in dry diglyme (80 ml), was passed in a *slow* stream of dry nitrogen through a wash-bottle containing sodium borohydride (0·5 g) in dry diglyme (30 ml) and then through a solution of the acid (9) (1·28 g) in dry THF (100 ml). When the addition of iodine was completed the generator flask and washing solution were heated in oil baths at 70° for 1 h. After standing at 20° for 1 h the complex was treated with methanol (100 ml) and heated under reflux for 30 min. Removal of solvent under reduced pressure gave a green oil (0·8 g). Chromatography on Woelm silica (50 g) and elution with ether gave the alcohol (1b) which crystallised from benzene (0·6 g, 55%) m.p. 86—87°.

7-*Methoxy*-1,2,3,4-*tetrahydrocarbazole* (3b).—4-(6-Methoxyindol-3-yl)butan-1-ol (1·5 g) with freshly distilled boron trifluoride–ether (55 ml) was heated under reflux for 40 min. The mixture was then poured into water (75 ml) and extracted with chloroform (2 × 100 ml). The extract was washed with water, dried ($MgSO_4$), and the solvent removed under reduced pressure to give a gum (1·5 g). Chromatography over Mallinckrodt silicic acid (100 mesh) (75 g) and elution with ether afforded the crude tetrahydrocarbazole (0·35 g). Two crystallisations from absolute ethanol gave the pure tetrahydrocarbazole (3b) (0·18 g), m.p. 146—147° (measured in dark), (lit.,[6] 146°), τ 8·15 (4H, m, 2- and 3-CH_2), 7·37 (4H, m, 1- and 4-CH_2), 6·2 (3H, s, OMe), 3·28br (1H, s, 8-H), 3·23 (1H, partially obscured dd, *J* 9, 2 Hz, 6-H), 2·67 (1H, d, *J* 9 Hz, 5-H), and 2·54br (1H, s, NH), $\lambda_{max.}$ 230 (ε 32,600), 270 (4800), and 300 (5400) nm, *m/e* (%), 201 (M^+, 92), 186 (61), 173 (100), 158 (14), 130 (40), 115 (11), 103 (9), and 89 (9).

Effect of Hydrochloric Acid on the N.m.r. Spectra of the Tetrahydrocarbazoles (3a) *and* (3b).—A solution of the tetrahydrocarbazole (45 mg) in deuteriochloroform (0·4 ml) was exposed to dry HCl gas. The n.m.r. spectrum showed progressive changes from that described above which reached limiting values on repeating the exposure. The assignments for protonated 7-methoxytetrahydrocarbazole (3b) were τ 7·96 (4H, m, 2- and 3-CH_2), 7·85 (2H, m, 1-CH_2), 6·64 (2H, m, 4-CH_2); 6·12 (3H, s, OMe), 2·96 (1H, dd, *J* 9, 2 Hz, 6-H), 2·63br (1H, s, 8-H), and 2·5 (1H, d, *J* 9 Hz, 5-H). For the protonated tetrahydrocarbazole (3a) a similar experiment resulted in a spectrum with the assignments τ 8·0 (4H, m, 2- and 3-CH_2), 7·87 (2H, m, 1-CH_2), 6·7 (2H, m, 4-CH_2), and 2·2—2·8 (4H, complex m, Ar*H*).

Oxidation of 7-*Methoxytetrahydrocarbazole* (3b) *with Periodic Acid.*—7-Methoxytetrahydrocarbazole (0·52 g) in methanol (35 ml) was added dropwise with stirring to a solution of periodic acid (1·5 g) in water (3 ml) and methanol (6 ml) under nitrogen. The mixture was maintained at 0° during the addition and then stirred at 20° for 10 min. The mixture was then poured into water (150 ml) and extracted with chloroform (3 × 100 ml). The extract was washed with 0·1N-sodium thiosulphate solution (100 ml) followed by water (100 ml) and dried ($MgSO_4$). Removal of solvent under reduced pressure gave a dark brown oil. Chromatography on Woelm silica (60 g) and elution with light petroleum–ether (1 : 3) gave a yellow oil (0·11 g) which was purified by p.l.c. [ether–light petroleum (2 : 3)]. The faster moving band was eluted with chloroform and removal of solvent afforded the crude oxo compound. Two crystallisations from benzene gave 6-*iodo*-7-*methoxy*-3,4-*dihydrocarbazol*-1(2H)-*one* (11b) as a pale yellow solid (45 mg, 9%), m.p. 217—218°, τ 7·72 (2H, m, $COCH_2CH_2$), 7·40 (2H, t, *J* 7·5 Hz, $COCH_2$); 7·07 (2H, t, *J* 7 Hz, $COCH_2CH_2CH_2$), 6·07 (3H, s, OMe), 3·15 (1H, s, 8-H), and 1·92 (1H, s, 5-H), $\lambda_{max.}$ 216 (ε 23,440), 245 (19,050), 260 (17,380), and 335 (23,440) nm, $\nu_{max.}$ (Nujol) 3333 (NH), 1653 (C=O), and 1613 (C=C) cm^{-1}, *m/e* (%) 341 (M^+, 100), 326 (33), 298 (16), 285 (14), 215 (12), 199 (10), 184 (10), 143 (13), 128 (16), 115 (20), and 101 (10) (Found: C, 45·8; H, 3·5; N, 4·0; I, 37·4. $C_{13}H_{12}INO_2$ requires C, 45·7; H, 3·5; N, 4·1; I, 37·2%). After elution of the column with ether and concentration, the eluent slowly deposited 3,4,5,6-*tetrahydro*-9-*iodo*-10-*methoxy*-1H-1-*benzazonine*-2,7-*dione* (12b) as crystals (112 mg), m.p. 280° (decomp.), τ (CF_3CO_2H) 7·98 (4H, m, $COCH_2CH_2CH_2$), 7·46 (2H, m, $NHCOCH_2$), 6·92 (2H, m, $COCH_2$), 6·0 (3H, s, OMe), 3·17 (1H, s, 11-H), 1·75 (1H, s, 8-H), and 0·65br (1H, s, NH), $\lambda_{max.}$ 244 (ε 27,540) and 270 (16,980) nm, $\nu_{max.}$ (Nujol) 3390 (NH), 1681 (ArCO), and 1667 (NHCO) cm^{-1}, *m/e* (%) 359 (M^+, 2), 233 (25), 205 (22), 204 (33), 176 (10), 165 (25), 160 (14), 150 (100), 149 (43), 122 (18), and 107 (20) (Found: C, 42·8; H, 3·9; N, 3·8; I, 35·6%. $C_{13}H_{14}INO_3$ requires C, 43·0; H, 3·9; N, 3·9; I, 35·4%).

[1-^{3}H]-4-(6-*Methoxyindol*-3-*yl*)*butan*-1-*ol*.—The acid (9) was reduced with tritated diborane essentially as described above for the untritiated compound, but in this case from sodium borotritide (2·5 mg; 2·5 mCi). The diborane

generator was charged first with one half of the inactive borohydride, then with the tritiated borohydride, and finally with the remainder of the inactive borohydride. In this way 6-methoxyindol-3-ylbutyric acid (0·6 g) was converted to the tritiated alcohol. After crystallisation from benzene, *ca.* 0·1 g (18%) of highly active material was obtained, m.p. 86—86·5°. After preliminary exploratory small-scale dilutions, the highly active alcohol (100 mg) was diluted with inactive material (1b) (5 g) and the mixture was crystallised from benzene to give a less active sample (4·8 g) m.p. 86—86·5°, $7·4 \times 10^8$ c mol^{-1} min^{-1}. After four crystallisations the material gave constant activity of $7·7 \times 10^8$ c mol^{-1} min^{-1}.

Cyclisation of [1-^{3}H]-4-(6-*Methoxyindol*-3-*yl*)*butan*-1-*ol*.—The diluted radioactive alcohol described above (0·5 g) was refluxed with boron trifluoride–ether (freshly distilled; 20 ml) for 30 min. The mixture, after cooling, was poured into water (100 ml) and extracted with chloroform (3 × 80 ml). Inactive tetrahydrocarbazole [6] (3b) (1·5 g), m.p. 146—147° (in dark), was added to the chloroform solution which was washed with water (100 ml), dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a green oil (1·86 g) which solidified on keeping at 20°. Chromatography over Mallinckrodt silicic acid (150 g) and elution with ether gave the crude product which crystallised from ethanol (1·25 g), m.p. 144—147° (in dark). Recrystallisation (×6) gave material of constant activity $9·89 \times 10^8$ d mol^{-1} min^{-1}, m.p. 146—147° (in dark).

Oxidation of the Radioactive Tetrahydrocarbazole.—The above radioactive tetrahydrocarbazole (0·98 g) in methanol (65 ml) was added dropwise to a solution of periodic acid (3 g) in water (6 ml) and methanol (14 ml) at 0°. The mixture was stirred at 0—5° for 15 min. T.l.c. then showed only faint traces of starting material. Work-up as for inactive material gave a brown oil (0·94 g). P.l.c. as described for the inactive material gave the radioactive iodo-oxo-compound (11b) as a semi-solid (0·11 g). Repeated chromatography gave material (70 mg), m.p. 207—211°, which was crystallised from benzene (×5) to constant activity of $3·81 \times 10^8$ d mol^{-1} min^{-1}, m.p. 219—220°. Two further experiments were carried out on a different batch of radioactive alcohol in refluxing boron trifluoride–ether for 45 min and at 100° for 45 min. For reflux for 30 min, the ratio of the molar activity of dihydrocarbazolone (11b) to the molar activity in tetrahydrocarbazole (3b) was 0·385, for reflux for 45 min, 0·477, and for heating at 100° for 45 min, 0·430. It can be shown that if x is the percentage of the alcohol (1b) which reacts by 'direct' initial attack at the 2-position of the indole (path A, Scheme 1) then the ratio of the molar activity of the dihydrocarbazolone (11b) to the molar activity of the tetrahydrocarbazole (3b) is given by $(100 - x)/200$.

Oxidation of 7-*Methoxytetrahydrocarbazole* (3b) *with Sodium Metaperiodate*.—The tetrahydrocarbazole (0·52 g) in methanol (35 ml) was added dropwise with stirring to a solution of sodium metaperiodate (1·98 g) in water (3 ml) and methanol (6 ml) under nitrogen; after 15 min a white precipitate appeared. After keeping overnight the mixture was poured into water (150 ml) and extracted with chloroform (3 × 100 ml). The extract was washed with 0·1N-sodium thiosulphate solution (100 ml) and water (100 ml), dried ($MgSO_4$), and the solvent was removed under reduced pressure to leave a brown oil. Chromatography on Woelm silica (70 g) and elution with ether afforded 3,4,5,6-*tetrahydro*-10-*methoxy*-1H-1-*benzazonine*-2,7-*dione* (12a) (0·126 g) m.p. 180° (decomp., softens at 165°), τ (CF_3CO_2H) 8·0 (4H, m, 4- and 5-CH_2), 7·46 (2H, m, 3-CH_2), 6·9 (2H, m, 6-CH_2), 6·04 (3H, s, OMe), 3·04 (1H, d, *J* 2 Hz, 11-H), 2·85 (1H, dd, *J* 9, 2 Hz, 9-H), 2·19 (1H, d, *J* 9 Hz, 8-H), and 0·6br (1H, s, NH). This spectrum slowly changed on keeping at 20°, eventually (*ca.* 1 month) becoming identical to that of the quinolone (13) (see below), $\lambda_{max.}$ 218sh (ε 21,200) 238 (22,600), and 270 (15,400) nm, $\nu_{max.}$ (Nujol) 3200 (NH), 1678 (ArC=O), and 1603 (NH–C=O) cm^{-1}, *m/e* (%) 233 (M^+, 24), 215 (11), 214 (13), 205 (24), 204 (30), 178 (7), 176 (14), 165 (24), 151 (11), 150 (100), 149 (33), 123 (8), 122 (7), and 107 (6) (Found: C, 67·2; H, 6·6; N, 5·6. $C_{13}H_{15}NO_3$ requires C, 66·9; H, 6·5; N, 6·0%).

Later fractions from the chromatography gave a mixture of the oxo-amide (12a) and its iodo-derivative (12b) from which fractional crystallisation from methanol afforded the iodo-oxo-amide (12b) (99 mg) identical by t.l.c., m.p. an mixed m.p., and n.m.r. spectrum with the sample described above. The oxo-amide (145 mg) was heated in an oil bath at 190° for 20 min. The solid first melted but then resolidified. Crystallisation from ethanol gave a solid (56 mg) which on sublimation at 0·5 mmHg gave 2,3-*dihydro*-6-*methoxy*-1H-*cyclopenta*[b]*quinolin*-9(4H)-*one* (13), which decomposed without melting at *ca.* 310°, τ (CF_3CO_2H), 7·54 (2H, quintet, *J* 7 Hz, 2-CH_2), 6·78 (2H, t, *J* 7 Hz, 1-CH_2), 6·60 (2H, t, *J* 7 Hz, 3-CH_2), 5·95 (3H, s, OMe), 2·74 (1H, d, *J* 2 Hz, 5-H), 2·60 (1H, dd, *J* 9, 2 Hz, 7-H), and 1·64 (1H, d, *J* 9 Hz, 8-H), $\lambda_{max.}$ 322 (ε 2205), 310 (2370), 298sh (1760), 254 (7610), 247 (6500), and 227 (1530) nm, *m/e* (%) 215 (M^+, 76), 214 (100), 200 (8), 199 (7), 172 (12), 144 (5), 143 (5), 142 (5), 115 (6), 108 (8), 78 (5), 77 (8), 65 (6), 63 (9), and 36 (9) (Found: M^+, 215·0944. $C_{13}H_{13}NO_2$ requires *M*, 215·0946). A completely satisfactory elemental analysis could not be obtained but the compound was shown to be homogeneous by t.l.c. and n.m.r.

[1,1-$^2H_2$]-4-(6-*Methoxyindol*-3-*yl*)*butan*-1-*ol* (1b).—4-(6-Methoxyindol-3-yl)butyric acid (2·5 g) in dry THF (50 ml) was added dropwise to a suspension of lithium aluminium deuteride (LAD) (1 g) in THF (50 ml). When the addition was complete the mixture was refluxed for 15 min. when t.l.c. showed the reaction to be complete. Excess of LAD was decomposed with a saturated solution of Rochelle salt; the mixture was poured into water (100 ml) and extracted with ether (2 × 100 ml). The ether layer was washed with water (100 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give the *deuteriated alcohol* (1b) (2·48 g) which was recrystallised from benzene (×2) to give cream plates (2·05 g, 86%) m.p. 87—87·5°. The n.m.r. spectrum was identical with that of the non-deuteriated compound (1b) except that the signal at τ 6·39 was entirely absent indicating complete deuteriation, *m/e* (%) 221 (M^+, 33), 162 (5), 161 (26), 160 (100), 149 (5), 145 (10), and 117 (8) (Found: *M*, 221·1385. $C_{13}H_{15}D_2NO_2$ requires *M*, 221·1385).

Cyclisation of the Deuterio-alcohol (1b) *with Boron Trifluoride–Ether*.—The deuteriated alcohol (1b) (1·5 g) was heated at 80° with boron trifluoride–ether (freshly distilled; 50 ml) for 1 h. The product was worked up as previously described for the non-deuteriated alcohol. A light green oil was obtained which was chromatographed on Mallinckrodt silicic acid (100 g) as previously described. The crude deuteriated tetrahydrocarbazoles were obtained as a light green solid (0·27 g). A crystalline specimen was obtained, m.p. 127—129°, on which n.m.r. analysis indicated that the combined proton resonances at C-1 and C-4

were 50% of those at C-2 and C-3. Other signals were identical to those in non-deuteriated tetrahydrocarbazole.

Oxidation of the Deuteriated Tetrahydrocarbazoles.—The above mixture of tetrahydrocarbazoles (0·27 g) in methanol (21 ml) was added dropwise to a suspension of sodium metaperiodate (1·3 g) in water (1·8 ml) and methanol (3·6 ml) under an atmosphere of nitrogen. The nitrogen flow was stopped and the mixture stirred overnight at 20°. After working up as for the nondeuteriated compound a brown oil was obtained. Chromatography over Woelm silica (70 g) gave the deuteriated oxo-amides (12a) as crystals (66 mg). The n.m.r. spectrum, measured in trifluoroacetic acid immediately after dissolving the solid, showed that the ratio of protons at C-3 and C-6 was 0·58. Another similar experiment gave the ratio 0·57. It can be shown that if x is the percentage of the alcohol (1b) which reacts by ' direct ' attack at the 2-position of the indole (path A, Scheme 1) then the ratio of hydrogen at the 3 position relative to that at the 6-position in the mixture of deuteriated oxo-amides (12a) = $(100 - x)/(100 + x)$.

Cyclisation of [1-^{3}H]-4-(6 *Methoxyindol-3-yl*)*butan-1-ol Tosylate to 7-Methoxy-1,2,3,4-tetrahydrocarbazole.*—To radioactive 6-methoxyindol-3-ylbutanol (0·4 g), dissolved in dry pyridine (10 ml) at −40°, was added a solution of toluene-*p*-sulphonyl chloride (0·35 g) in dry pyridine (5 ml) cooled to −10° under an atmosphere of nitrogen. The mixture was kept at −50° for 6 h. T.l.c. showed that most of the alcohol had then reacted; and in addition to 7-methoxytetrahydrocarbazole there was an intermediate spot at the R_F expected of the tosylate. The pyridine was extracted with cold n-pentane; the residue (0·45 g) was then dissolved in the minimum of acid-free chloroform and chromatographed over Florisil (35 g). Elution with benzene yielded a bluish pink fluorescent band which on removal of solvent gave active 7-methoxytetrahydrocarbazole (3b) (0·28 g, 70%), m.p. 143—145°. Further elution with benzene–ether mixtures gave unreacted alcohol and polymeric materials. The active 7-methoxytetrahydrocarbazole was diluted with inactive material, and crystallised and sublimed to constant activity of $3{\cdot}38 \times 10^8$ d mol^{-1} min^{-1}. Oxidation of the active tetrahydrocarbazole as described, above, with periodic acid gave 6-iodo-7-methoxydihydrocarbazole-1(2*H*)-one (11b) which was crystallised to constant activity of $1{\cdot}24 \times 10^8$ d mol^{-1} min^{-1}. Hence the ratio of the molar activity of the iododihydrocarbazolone to that of the tetrahydrocarbazole = 0·365.

We thank the S.R.C. for a maintenance grant (to R. I.) and for assistance in purchasing the mass spectrometer.

[2/2681 *Received, 27th November,* 1972]